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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,754	01/08/2002	Norbert Hampp	18744-0001	5299

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EXAMINER	
HANLEY, SUSAN MARIE	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,754	HAMPP ET AL.	
	Examiner	Art Unit	
	Susan Hanley	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 9-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *7 and 8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date ~~3/6/2002~~. 2/22/02
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Suggestion

It is suggested that the phrase "is reacted which" in claims 5-8 be deleted for ease of reading.

Claim Objections

Claims 2 and 4-16 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim could refer to another claim in the alternative only and/or cannot depend from any other multiply dependent claim. See MPEP § 608.01(n). However, the claims have been examined on their merits as if they depend from another claim in the alternative.

Claim 13 is objected to because it appears to be a Markush claim that is in improper format. It is suggested that the claim read as follows: "the auxiliary substance is selected from the group consisting of dyes ...".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9 and 15-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "briefly" in claim 9 is a relative term which renders the claim indefinite. The term "briefly" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Regarding claim 5, the phrase "in particular" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claims 15 and 16 provide for the use of a linker-free, covalently cross-linked bacteriorhodopsin, but, since the claim does not set forth any steps involved in the method/process, it is unclear what

method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 15 and 16 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966). The claims will be treated as process claims and will be examined as depending from claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6 and 9-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takeda et al. (US 5,252,719) or Smithey et al. (6,140,012) in view of the combination of Gaffney (1985), Dutton et al. (1975), Kobayashi et al. (6,472,182) and Lehninger (1975).

Takeda et al disclose an oriented purple membrane from Bacteriorhodopsin and a method of making thereof. The protein used may also be halorhodopsin, as in claim 5, (col. 4, lines 45-50). The protein molecules are oriented in the membrane by electrophoresis or an antigen-antibody reaction. The membranes are then cross-linked by a chemical reagent, as in claim 1, (col. 3, lines 1-10) to impart stability to the oriented membrane. The process causes the formation of a three-dimensional structure comprising successive layers of oriented purple membrane (col. 3, lines 10-25). The multi-layer structure can be used as a photoelectric transducer (col. 1, lines 7-12), as in claim 15.

Smith et al. disclose that bacteriorhodopsin can be modified or engineered by making alterations in the amino acid sequence of the wild type protein in order to improve its photochromic effects (col. 1, lines 55-65), as in claim 6. Bacteriorhodopsin variants can be stabilized by contacting them with a chemical

crosslinking in order to link the membranes together (as in claims 1-??). The membranes can also be coupled to a polymer (col. 4, lines 30-44), as in claims . The cross-linked membranes are useful for storing digital and analog optical data (col. 2, lines 20-30), as in claim 16.

Neither Takeda et al. not Smithey et al. disclose that Bacteriorhodopsin the purple membrane form can be cross-kinked to itself or other substances by a transglutaminase that can have a bacterial origin, is active without a cofactor or that the enzyme ceases its catalytic activity at about 80 degrees. Nor do the references disclose that the bacteriorhodopsin variant contains only a single binding site for the transglutaminase.

Gaffney et al. disclose various cross-linking techniques and applications. Gaffney et al. teach that the employment of calcium-dependent transglutaminase as a cross-linker is an alternative to chemical reagents (p. 304). Since the agent is an enzyme, it catalyses a bond that is free of any part of the agent. Further, Bacteriorhodopsin in membrane form has been cross-linked by chemical agents (p. 311, left column).

Dutton et al. disclose that transglutaminase catalyzes the crosslinking of glutamine and lysine and is useful for crosslinking membrane-bound proteins to each other or modifying membrane proteins with a substance (p. 2568, left column). Dutton et al. teach that cross-linking of intact membrane proteins has several advantages over chemical methods. Enzymatic reactions are very mild and the extent of modification is relatively small compared to chemical agents. Transglutaminase is a more specific agent compared to chemical agents since only protein-bound glutamyl residues are acceptor sight for cross-linking reaction. Furthermore, the specificity of transglutaminase-catalyzed reactions is their membrane sidedness. Chemical cross-linking agents are known to penetrate membranes. Cellular membranes are impermeable to transglutaminase. Hence, the enzyme will modify residues that are exposed at the surface of the membrane (p. 2570-1, bridging paragraphs). Dutton et al. also relate that the specificity of transglutaminase probably allows for a few, or perhaps one, exposed glutamyl residue on a given membrane to become labeled.

McDowell et al. relate that transglutaminase successfully modified rhodopsin in outer segment disk membrane by linking primary amines to glutamine residues. In order to avoid formation of protein

crosslinks, rhodopsin was reductively methylated to modify its lysine residues so that the glutamyl residues could be linked with putrescine, ethanolamine or dinitrophenylcadaverine (abstract).

Kobayashi et al. teach that transglutaminase can be mass-produced at a low cost from a number of bacterial sources and does not require calcium for activity. This is advantageous because transglutaminase derived from animals requires calcium which, therefore, limits their application (col. 1, lines 35-65). Kobayashi et al. also teach that bacterial transglutaminases are active as long as the substrate(s) have accessible lysyl and glutamyl residues (col. 5, lines 50-65).

Lehninger teaches that enzyme-catalyzed reactions have an optimum temperature for activity that decreases with increasing temperature. The loss of activity past the optimum temperature is due to thermal denaturation of the enzyme. Many enzymes are inactivated at 55-60 degrees. However, some enzymes are known to remain active beyond 85 degrees (p. 197).

It would have been obvious to one of ordinary skill at the time the invention was made to employ a bacterial transglutaminase to cross-link bacteriorhodopsin, or variants thereof, in the purple membrane form, wherein the enzyme does not require a cofactor for activity and whose activity can be stopped at 80 degrees. The ordinary artisan would have been motivated to replace a chemical crosslinking agent with transglutaminase because it has been shown that said enzyme can form intermolecular and intramolecular bonds between lysyl and glutamyl residues in membrane-bound proteins to achieve linker-free membrane proteins. Transglutaminases lack the harshness and lack of specificity associated with chemical crosslinkers. These characteristics are desirable for cross-linking substances in delicate biological systems. Since it was known that bacteriorhodopsin could be linked by chemical crosslinkers and that the necessary lysyl and glutamyl residues are exposed at the membrane-bound protein, the ordinary artisan would have had a reasonable expectation that transglutaminase could successfully cross-link bacteriorhodopsin in the purple membrane form. Furthermore, it was known at the time the invention was made that transglutaminase could successfully link membrane proteins in the disc form such as rhodopsin as well as other systems having proteins embedded in membranes.

The ordinary artisan would have been motivated to employ a bacterial transglutaminase to catalyze the reaction and to stop the reaction at 80 degrees because bacterial transglutaminases are cheaply and readily available on the commercial market. Thus, the enzyme would be convenient and not costly. The

bacterial transglutaminases inherently do not require a cofactor. The ordinary artisan would have had a reasonable expectation that the bacterial enzymes would successfully crosslink rhodopsin in the purple membrane form because the necessary residues are exposed at the surface of the membrane which are the minimum requirements set forth by Kobayashi et al for catalysis.

Allowable Subject Matter

Claims 7 and 8 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Hanley whose telephone number is 571-272-2508. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JEAN C. WITZ
PRIMARY EXAMINER